

## Clinical Research

# Interictal Spikes Increase Cerebral Glucose Metabolism and Blood Flow: A PET Study

R. G. Bittar, F. Andermann, A. Olivier, F. Dubeau, S. O. Dumoulin, G. B. Pike, and  
D. C. Reutens

Montreal Neurological Institute and Hospital, and Department of Neurology and Neurosurgery, McGill University,  
Montreal, Quebec, Canada

**Summary:** *Purpose:* In patients with reflex epilepsy, it is sometimes possible to evoke interictal spikes predictably, thus providing an uncommon but important experimental paradigm for examining the physiological changes produced by epileptiform discharges.

*Methods.* To examine the changes in regional cerebral blood flow (rCBF) and glucose consumption (rCMRglc) produced by interictal spikes, we performed positron emission tomography (PET) scans with the blood-flow tracer [ $^{15}\text{O}$ ]H $_2$ O and with [ $^{18}\text{F}$ ]fluorodeoxyglucose in a patient with fixation-off epilepsy. The scans were performed in states of high and low spike frequency produced by eye closure and opening, respectively.

*Results:* The rCBF study revealed a focal increase in blood flow associated with the state of increased interictal spiking. The focus was in the posterior portion of the left superior

parietal lobule (Talairach coordinates: x: -36, y: -71, z: 39;  $t = 4.5$ ;  $p < 0.05$ ) and corresponded to the site of maximal ictal EEG abnormality recorded with implanted electrodes. In a volume of interest of 10-mm diameter centered on the  $t$  statistic peak in the rCBF study, the mean rCMRglc was 39.1  $\mu\text{mol}/100 \text{ g}/\text{min}$  with eyes open and 44.1  $\mu\text{mol}/100 \text{ g}/\text{min}$  (13% increase) with eyes closed. An identical activation paradigm was used in six normal subjects studied with functional magnetic resonance imaging. In the normal subjects, no significant activation was observed in the parieto-occipital region, indicating that the changes observed in the patient were due to interictal spiking rather than to task performance alone.

*Conclusions:* Interictal spiking produces focal increases in cerebral blood flow and glucose metabolism. **Key Words:** Epilepsy—Interictal spikes—PET—Glucose—Energy.

The energy requirements of interictal spike discharges remain incompletely understood. In the majority of cases of adult temporal lobe epilepsy, interictal [ $^{18}\text{F}$ ]fluorodeoxyglucose (FDG) uptake is reduced (1-8), despite the presence of interictal spikes. However, a number of patients with increased focal glucose metabolism during interictal spike activity have now been reported (2,9,10). Additionally, in some animal models, interictal spikes have been shown to increase the regional metabolic rate for glucose (rCMRglc; 11). In general, it is difficult to study the metabolic effects of interictal spike discharges in humans because spike frequency can rarely be manipulated to suit a scanning schedule.

We describe a patient with fixation-off epilepsy in whom interictal spike frequency was modulated by eye closure. Positron emission tomography (PET) was used

to measure regional cerebral blood flow (rCBF) and rCMRglc during periods of high and low spike frequency.

## PATIENT REPORT

The patient, a right-handed man aged 42 years, was the product of an uncomplicated pregnancy and forceps delivery. He had no history of central nervous system trauma or infections, or of febrile convulsions. Seizures began at age 3 months and were characterized by an initial arrest of movement, bilateral blindness or blurred vision, followed by head and eye deviation to the right. When more prolonged, seizures were sometimes accompanied by rotation of the body to the right or tonic-clonic movements of the right arm and face. Seizures occurred up to 3-4 times per day and were sometimes precipitated by movement from darkness into a bright environment or vice versa. Antiepileptic medications (AEDs) included phenytoin (PHT), 300 mg/day; lamotrigine (LTG), 200 mg/day; and phenobarbital (PB), 130 mg/day.

Accepted August 17, 1998.

Address correspondence and reprint requests to Dr. D. C. Reutens at Department of Neurology, Austin and Repatriation Medical Centre, Heidelberg, Victoria 3084, Australia.

The neurologic examination was normal. Neuropsychological evaluation demonstrated a borderline level of general intelligence (full scale IQ, 71; verbal IQ, 66; performance IQ, 79). Mild diffuse cerebral atrophy was present on magnetic resonance imaging (MRI), but there was no evidence of cortical dysplasia or of other focal lesions.

### Electroencephalography (EEG)

Interictally, surface EEG revealed bisynchronous spikes, maximal in the left posterior quadrant, which were partially suppressed by eye opening and increased in frequency with eye closure (Fig. 1). Opening and closing the eyes in a dark environment did not affect the EEG, and in a fully lit environment, the interictal spiking increased in frequency when a sheet of paper was placed in front of his eyes to eliminate fixation. Prolonged video-EEG monitoring with intracranial electrodes was performed. A neurosurgical guidance system (The Viewing Wand; ISG Inc., Mississauga, ON, Canada) was used to place the intracranial electrodes with the assistance of high-resolution MR images and coregistered images from the PET activation study described later. The electrodes were placed in the posterior hippocampus, the temporooccipital junction, and the supracalcarine occipital regions bilaterally. The left occipital depth electrode passed through the region of PET activation. Interictal abnormalities consisted of frequent high-amplitude polyspike and slow wave discharges with focal accentuation over the left posterior temporal and occipital cortex. Epileptiform discharges were more prominent with eye closure. Seizures usually showed bilateral onset, often with focal accentuation in the left temporooccipital or occipital region (Fig. 2).

### Positron emission tomography (PET)

We compared rCBF and rCMRglc in a state of high spike frequency produced by eye closure and in a state of low spike frequency produced by eye opening. On 2 separate days, [ $^{15}\text{O}$ ]H $_2$ O and [ $^{18}\text{F}$ ]FDG PET scans were performed with a Scanditronix PC-2048 15B eight-ring scanner, which produces 15 slices with an intrinsic resolution of 6 by 6 mm. For each scan session, a foam head mold was fitted to minimize head movement. A [ $^{68}\text{Ge}$ ] orbiting rod transmission source was used for attenuation correction. The EEG was recorded continuously during the scans, and the patient was closely observed during the scanning and questioned afterward regarding clinical seizure manifestations. None were observed or reported. When the subject's eyes were open, he was asked to fixate on a point located 1.5 m in front of his face.

During the first scanning session, three PET scans were performed with [ $^{15}\text{O}$ ]H $_2$ O (40 mCi/injection) with eyes closed and three with eyes open in a quiet, moderately darkened room (to minimize activation of the occipital cortex). Each activation and baseline scan was

normalized by the mean whole brain value, to correct for global changes in blood flow. A *t* statistic map of changes in rCBF between scans with eyes closed and with eyes open was generated, and sites of significant changes in rCBF were determined. *t* Statistic volumes were generated from images of the mean change in regional cerebral blood flow by dividing each voxel by the average standard deviation pooled across voxels (12). The statistical significance of *t* statistic peaks was determined by a method based on three-dimensional gaussian random field theory (13). Peaks were considered statistically significant if their corresponding *p* value was <0.05. During the second scanning session, we used a quantitative, single-scan, double-injection method, allowing the determination of the change in rCMRglc between two physiological states (14,15). For this study, a short indwelling catheter was placed into the left radial artery for blood sampling. After the first injection (3 mCi [ $^{18}\text{F}$ ]FDG) the patient remained with eyes opened for 30 min. Then 2 mCi [ $^{18}\text{F}$ ]FDG was injected with the patient's eyes closed for 30 min. Plasma samples were taken every 10 s for the first 3 min after each [ $^{18}\text{F}$ ]FDG injection and then at increasingly prolonged intervals for the remainder of the scan. Plasma radioactivity and glucose concentration were measured in sampled arterial blood. By using previously described methods of analysis (14,15), the net uptake constant (*K*) was estimated for each portion of the scan, and mean rCMRglc was calculated for a volume of interest 10 mm in diameter centered on the *t* statistic peak identified in the rCBF activation study.

A  $T_1$ -weighted MRI scan (TR = 18 ms; TE = 10 ms; flip angle, 30°) yielding ~170 256 × 256 sagittal images comprising 1 mm<sup>3</sup> voxels was acquired. The MRI and PET images were then mapped into a common standard space by using automated algorithms based on a cross-correlation measure (16,17) to allow localization of the PET activation focus.

### Functional magnetic resonance imaging

Functional magnetic resonance imaging (fMRI) was performed in six normal subjects. These scans were obtained with the eyes closed (activation), followed by eye opening and visual fixation on a dot placed on a screen 1.5 m from their eyes (baseline). Multislice  $T_2$ -weighted gradient echo EPI (echo-planar imaging) images (TR/TE = 3.6 s/45 ms, excitation pulse angle = 90°) were acquired with a Siemens Magnetom Vision 1.5T MRI. To study the area between the cerebellum and the vertex, 10–12 contiguous 5-mm slices were obtained parallel to the calcarine sulcus. A total of 120 measurements (time frames) was acquired continuously with alternating baseline and activation conditions (three activation scans; three baseline scans) giving a total scanning time of ~7 min. In all subjects,  $T_1$ -weighted anatomic MRI images

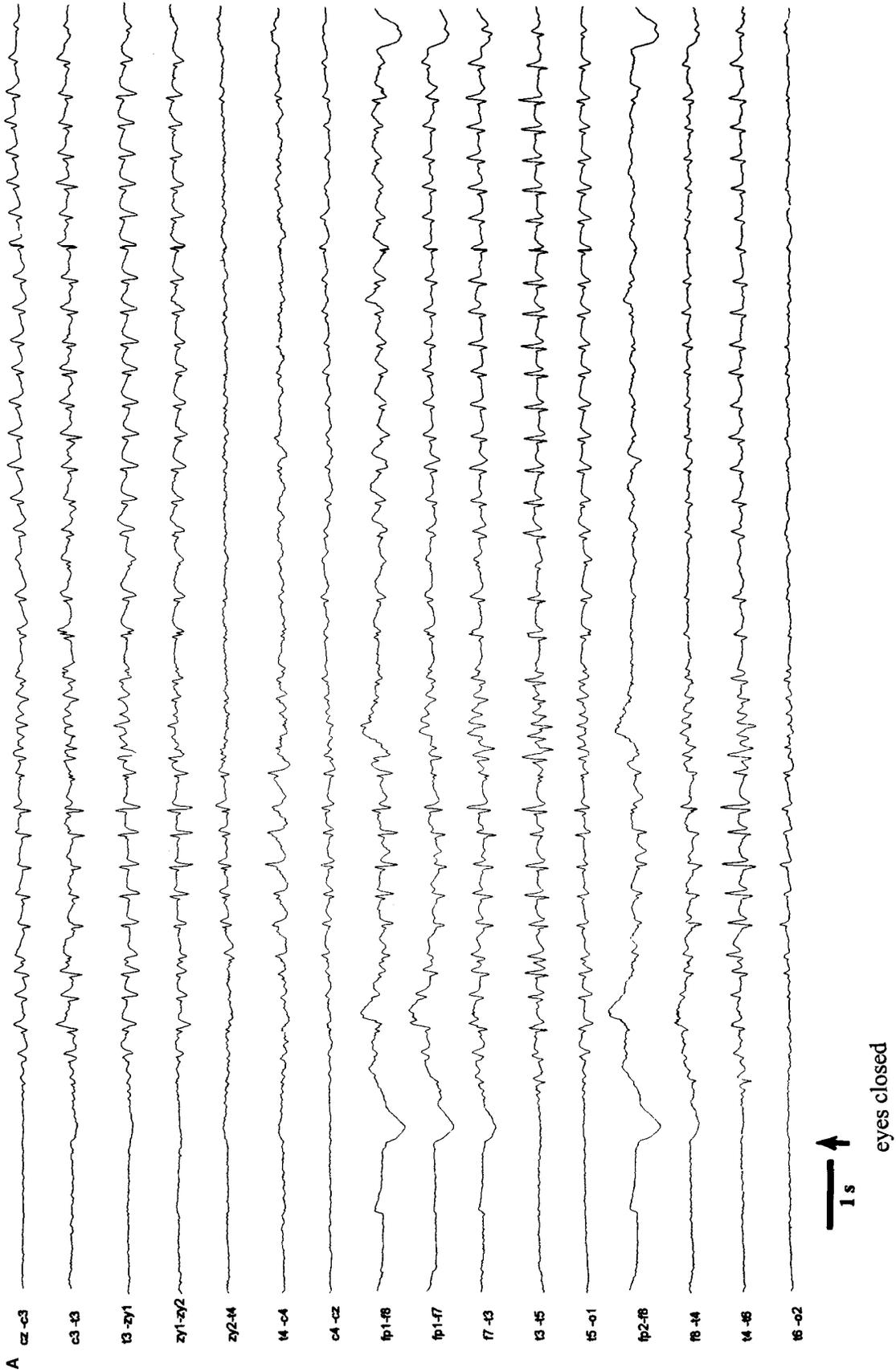


FIG. 1. Surface EEG showing interictal spikes occurring bisynchronously, with a left posterior quadrant predominance. Epileptiform discharges are precipitated by eye closure (A) and suppressed by eye opening (B).

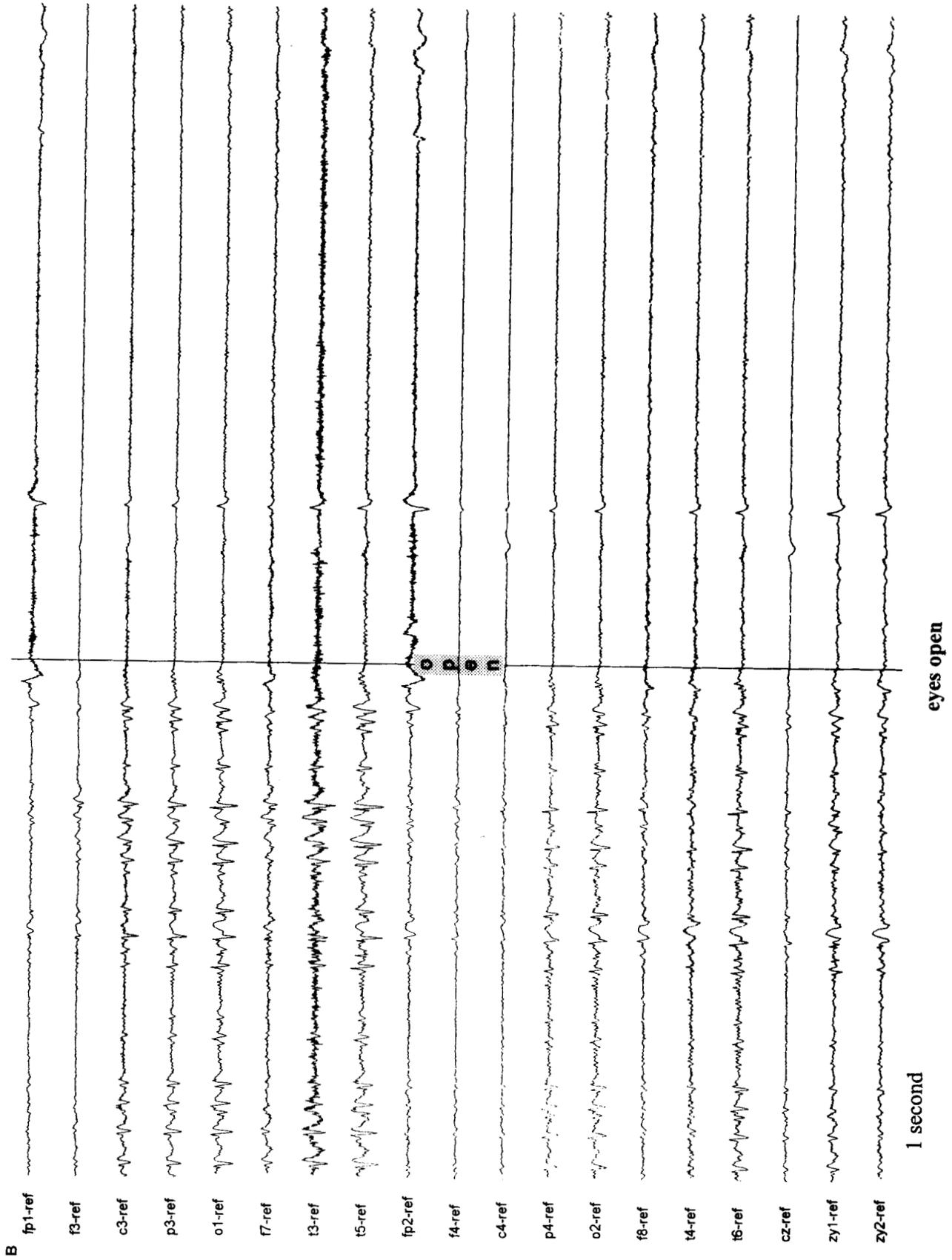
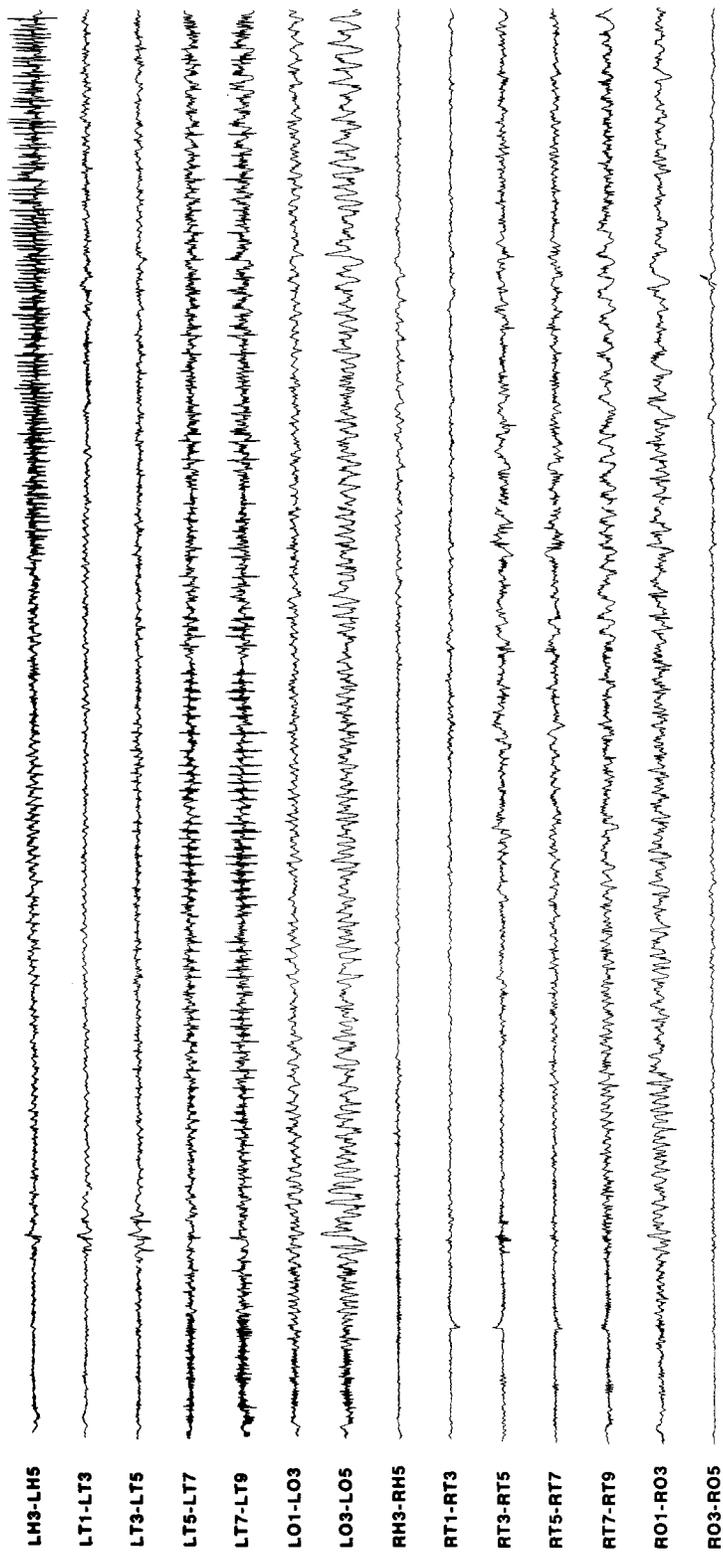


FIG. 1. Continued.



**FIG. 2.** Ictal discharge recorded with implanted electrodes. Seizures usually showed bilateral onset, often with focal accentuation in the left temporooccipital and occipital regions. Activity in the left hippocampus (LH3-LH5); right hippocampus (RH3-RH5); the deep to superficial contacts of the left and right posterior temporal electrodes (LT1 to LT9 and RT1 to RT9, respectively); and the deep to superficial contacts of the left and right occipital electrodes (LO1 to LO5 and RO1 to RO5, respectively) is shown.

were acquired by using a three-dimensional gradient-echo sequence ( $T_R = 18$  ms;  $T_E = 10$  ms; flip angle,  $30^\circ$ ) yielding  $\sim 170 \times 256 \times 256$  sagittal images comprising  $1 \text{ mm}^3$  voxels. Head position was fixed by a foam headrest and straps. All studies were performed with the informed consent of the patients and subjects and were approved by the institutional research ethics committee.

## RESULTS

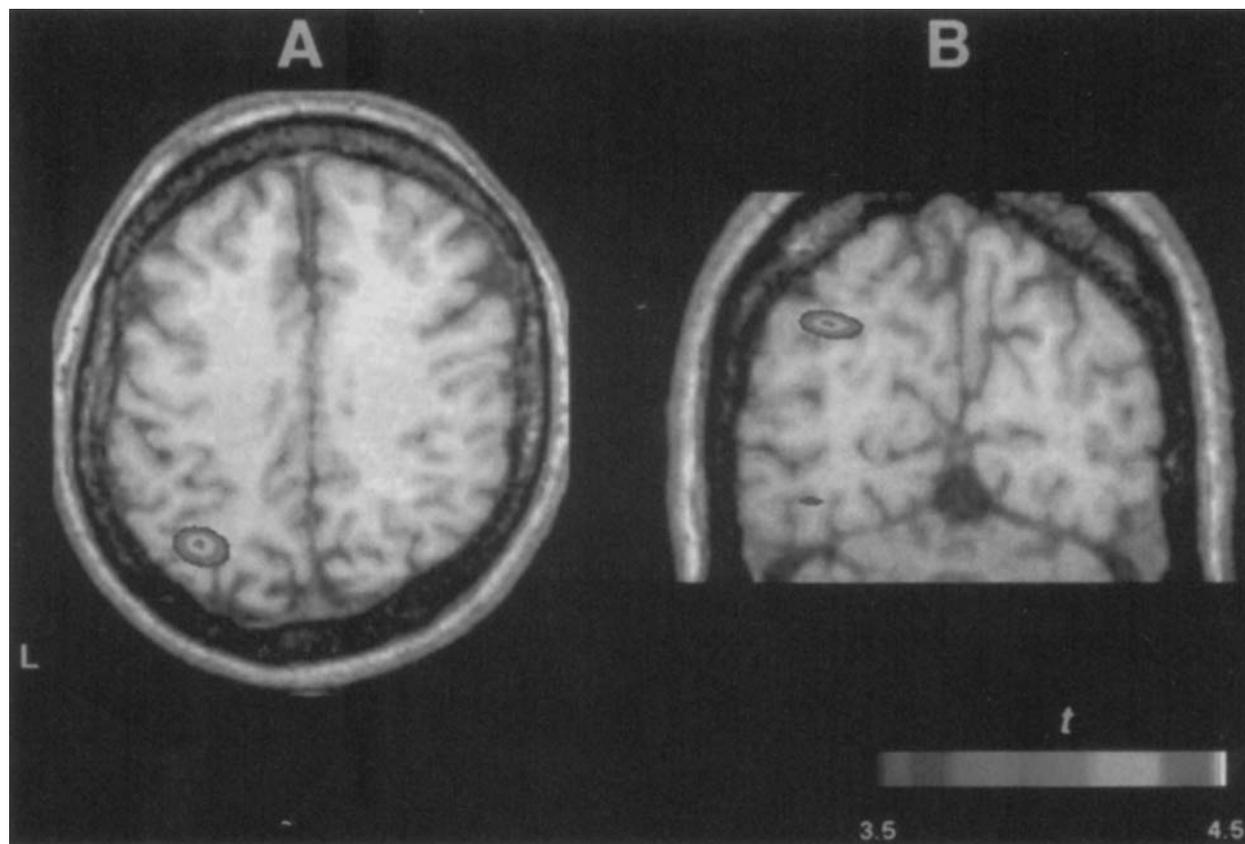
In the rCBF activation study, the mean spike frequency during eyes-open scans was 17/min. During scans with the eyes closed, the mean spike frequency was 44/min. A significant change in rCBF (34.6% increase) was observed in the posterior portion of the left superior parietal lobule ( $t = 4.5$ ;  $p < 0.05$ ) with the peak voxel located at Talairach coordinates (18): 36,  $-71$ , 39 (x, y, z mm; Fig. 3). There were no other statistically significant ( $p < 0.05$ ) activation peaks.

In the rCMRglc study, there were 432 spikes during the scan frames with eyes open and 1,003 during the scan frames with eyes closed. In the volume of interest, mean rCMRglc was  $39.1 \mu\text{mol}/100 \text{ g}/\text{min}$  with eyes open, and  $44.1 \mu\text{mol}/100 \text{ g}/\text{min}$  (13% increase) with eyes closed. With the eyes-closed minus eyes-open paradigm, all six

normal subjects displayed a strong negative activation peak in the occipital cortex surrounding the calcarine sulcus on fMRI. In the normal subjects, no positive activation peaks were observed in the region of the left hemisphere corresponding to the focus of PET activation observed in the patient.

## DISCUSSION

The PET studies in this patient were of interest because the ability to modulate the frequency of interictal epileptiform activity allowed us to study the blood-flow and metabolic changes associated with interictal spikes. Seizures in this patient began with visual manifestations, and were sometimes precipitated by changes in the level of background illumination. We recorded interictal and ictal epileptiform abnormalities, which were bisynchronous but maximal in the left occipital region, and which were more active with eye closure. PET studies revealed increased rCBF and rCMRglc during periods of increased interictal spiking in a region corresponding to the site of maximal ictal EEG abnormality recorded with implanted electrodes. One electrode was passed through the region of PET activation with the assistance of a surgical-guidance device and coregistered PET and MRI



**FIG. 3.**  $t$ -Statistic map of PET study with  $[^{15}\text{O}]\text{H}_2\text{O}$ . A focus of significant change in blood flow between the eyes-closed and eyes-open state is observed in the posterior portion of the left superior parietal lobule (Talairach coordinates: x,  $-36$ ; y,  $-71$ ; z, 39;  $t = 4.5$ ;  $p < 0.05$ ).

scans. In our hands, the spatial error of the guidance device is <3 mm (19).

Our finding of increased glucose metabolism associated with interictal spikes is similar to the finding by Handforth et al. (10) of focal increases in metabolism in periodic lateralized epileptiform discharges (PLEDs). Although the blood-flow and metabolic changes produced by interictal spikes are incompletely understood, there are considerable data on changes in [<sup>18</sup>F]FDG uptake and rCBF in the ictal and interictal states. Ictal studies with single photon emission computed tomography have shown that during seizures, rCBF increases focally in >70% of patients with temporal lobe epilepsy (20–22). Theodore et al. (8,23) demonstrated increased rCBF in both the thalamus and the temporal lobes during complex partial seizures.

Autoradiographic studies with [<sup>14</sup>C]deoxyglucose in rats demonstrated up to twofold increases in ictal glucose utilization at the site of the primary EEG discharge (24,25). In contrast, Engel et al. (26) observed both focal hypermetabolism and hypometabolism in patients with spontaneous partial seizures. The interpretation of ictal studies of FDG uptake may be complicated by the violation of steady-state assumptions resulting from metabolic changes in the ictal and postictal phases. The contribution of postictal depression may be responsible for apparent ictal hypometabolism. The pattern of blood-flow changes in absence seizures is likely to differ from that of partial seizures. During absence seizures, Prevett et al. (27) found both an increase in global blood flow and an additional selective increase in thalamic blood flow; however, Nehlig et al. (28) observed a decrease in rCBF.

The energy requirements and blood-flow changes produced by interictal spikes and by seizures need not necessarily be similar. The phenomena differ electrophysiologically. Interictal spikes are characterized by a paroxysmal depolarization shift of the resting membrane potential with bursts of action potentials. These are followed by a period of hyperpolarization and neuronal inhibition (29,30). In contrast, the transition from interictal to ictal discharges is characterized by the loss of afterhyperpolarization, the subsequent development of prolonged afterdepolarizations, and the appearance of multiple spike discharges (30–32). The energy requirements of each of these phases and their relative time-integrated contributions are not known.

No previous [<sup>18</sup>F]FDG PET studies in humans have incorporated a paradigm in which spike frequency was deliberately modulated. However, in four children with focal epilepsy, Chugani et al. (9) observed focal interictal hypermetabolism in regions of extremely frequent interictal discharge. In an interictal spiking model produced by systemic administration of bicuculline in the rat, Handforth et al. (11) demonstrated that interictal epi-

leptiform activity induced glucose hypermetabolism and found that hypermetabolism was significantly correlated with spiking frequency. In this model, which produced a spiking rate of 12–22 spikes per minute, there was a significant correlation between hypermetabolism and spiking rate. This finding may also, in part, explain the frequent absence in PET studies of increased metabolism with interictal spiking. In most clinical situations, a low spike frequency may be insufficient to produce a detectable increase in rCMRglc or even to compensate for the other countervailing influences on tracer uptake discussed later. In our study, it is notable that high spike frequencies were achieved (17 spikes per minute with eyes open, 44 spikes per minute with eyes closed).

Interictal FDG PET scans frequently show a focal reduction in tracer uptake. This is especially so in temporal lobe epilepsy, in which relative reductions in tracer uptake, greater in the lateral than the mesial temporal cortex ipsilateral to the seizure focus, occur in ≥90% of patients (33–35). Factors other than interictal discharges are likely to contribute to this finding. Indeed, previous studies failed to demonstrate a quantitative relation between the degree of focal hypometabolism and interictal spike frequency (1,2,36). In addition, the region of interictal hypometabolism may differ from the area of spiking in extent and, in some cases, localization. The hypometabolic zone often exceeds the size of the epileptogenic zone on EEG (36,37) and may even exclude the epileptogenic focus (38). The degree of hypometabolism may relate to the degree of cell loss in the neocortex (36), to diaschisis associated with hippocampal neuronal loss, or to synaptic reorganization in the epileptogenic region. The partial-volume effect produced by atrophy of the temporal lobe ipsilateral to the seizure focus also may give the appearance of hypometabolism.

The increase in CBF (34.6%) in our study was much greater than the increase in glucose metabolism (13%). There are two possible explanations for this. First, the CBF and CMRglc studies were conducted during separate scanning sessions on separate days. Second, there may truly be an uncoupling of glucose metabolism and blood flow in epileptogenic cortex, in both interictal (39,40) and ictal (41) states. The region of increased CBF in our study was much less extensive than the distribution of EEG changes. This apparent discrepancy is likely to be due to the statistical method used in the analysis of the PET data and the low statistical power to detect changes in rCBF. This was limited because of the restrictions placed on the number of repetitions of activation and baseline scans by dosimetric considerations.

Our findings cannot be explained simply by a regional reduction in rCBF during visual fixation, which would yield a positive peak with the eyes-closed minus eyes-open paradigm. fMRI studies in six normal subjects, using the same activation and baseline tasks as in the pa-

tient's PET study, failed to demonstrate a positive peak corresponding to the focus of activation in the superior parietal lobule in the patient. Furthermore, the cortical region activated during increased spiking correlated well with the site of ictal and interictal EEG abnormality on depth-electrode studies. From solid-angle theory, Gloor (42) noted that intracranial electrodes are biased in favor of proximal electrical sources to the detriment of others at a relatively short distance away. Hence, the interictal spikes detected in the intracranial electrode passing through the site of PET activation are likely to originate in generators close to the electrode.

Different functional neuroimaging techniques (PET and fMRI) were used to assess brain activation in the patient and in volunteers. Both methods indirectly measure neuronal activity, PET by measuring CBF changes, and fMRI by measuring changes in deoxyhemoglobin levels. The increase in blood flow to the region of neuronal activation exceeds the increase in oxygen consumption (43), and this uncoupling results in a reduced local deoxyhemoglobin concentration, the source of increased signal observed with blood oxygen level-dependent (BOLD) contrast MRI (44). Cross-validation of the two methods has revealed strong spatial agreement between the techniques (45,46).

In conclusion, we used PET to study rCBF and rCMRglc at different interictal spike frequencies produced by eye opening and closure in a patient with fixation-off epilepsy. Increased spike frequency was associated with a focal increase in blood flow and glucose metabolism.

**Acknowledgment:** Dr. Bittar was supported by a University of Sydney Faculty of Medicine Postgraduate Research Scholarship and a Thomas and Ethel Mary Ewing Travelling Fellowship.

## REFERENCES

- Kuhl DE, Engel J, Phelps ME, Selin C. Epileptic patterns of local cerebral metabolism and perfusion in humans determined by emission computed tomography of  $^{18}\text{F}$ FDG and  $^{13}\text{N}$  $\text{H}_3$ . *Ann Neurol* 1980;8:348-60.
- Engel J, Kuhl DE, Phelps ME, Mazziotta JC. Interictal cerebral glucose metabolism in partial epilepsy and its relation to EEG changes. *Ann Neurol* 1982;12:510-7.
- Sackellares JC, Abou-Khalil BW, Siegel GJ, et al. PET studies of interictal, ictal, and postictal changes in local cerebral blood flow in temporal lobe epilepsy. *Neurology* 1986;36(suppl 1):338.
- Abou-Khalil BW, Siegel GJ, Sackellares JC, Gilman S, Hichwa R, Marshall R. Positron emission tomography studies of cerebral glucose metabolism in chronic partial epilepsy. *Ann Neurol* 1987;22:480-6.
- Theodore WH, Fishbein D, Dubinsky R. Patterns of cerebral glucose metabolism in patients with partial seizures. *Neurology* 1988;38:1201-6.
- Chee MWL, Morris HH, Antar MA, et al. Presurgical evaluation of temporal lobe epilepsy using interictal temporal spikes and positron emission tomography. *Arch Neurol* 1993;50:45-8.
- Merlet I, Garcia-Larrea L, Gregoire MC, Lavenne F, Mauguiere F. Source propagation of interictal spikes in temporal lobe epilepsy: correlations between spike dipole modelling and [ $^{18}\text{F}$ ]fluorodeoxyglucose PET data. *Brain* 1996;119:337-92.
- Theodore WH, Newmark ME, Sato S, et al. [ $^{18}\text{F}$ ]Fluorodeoxyglucose positron emission tomography in refractory complex partial seizures. *Ann Neurol* 1983;14:429-37.
- Chugani HT, Shewmon DA, Khanna S, et al. Interictal and postictal hypermetabolism on positron emission tomography. *Pediatr Neurol* 1993;9:10-5.
- Handforth A, Cheng JT, Mandelkern MA, Treiman DM. Markedly increased mesiotemporal lobe metabolism in a case with PLEDs: further evidence that PLEDs are a manifestation of partial status epilepticus. *Epilepsia* 1994;35:876-81.
- Handforth A, Finch DM, Peters R, Tan AM, Treiman DM. Interictal spiking increases 2-deoxy[ $^{14}\text{C}$ ]glucose uptake and c-fos-like reactivity. *Ann Neurol* 1994;35:724-31.
- Evans AC, Marrett S, Neelin P, et al. Anatomic mapping of functional activation in stereotactic coordinate space. *Neuroimage* 1992;1:43-53.
- Worsely KJ, Evans AC, Marrett S, Neelin P. A three-dimensional statistical atlas for CBF activation studies in human brain. *J Cereb Blood Flow Metab* 1992;12:900-19.
- Reutens DC, Nishizawa S, Meyer E, Kuwabara H. A kinetic model for double injection  $^{18}\text{F}$ FDG studies. In: Myers R, Cunningham V, Bailey D, Jones T, eds. *Quantification of brain function using PET*. San Diego: Academic Press, 1996:214-8.
- Murase K, Kuwabara H, Meyer E, Evans AC, Gjedde A. Mapping of change in cerebral glucose utilisation using [ $^{18}\text{F}$ ]FDG double injection and new graphical analysis. In: Myers R, Cunningham V, Bailey D, Jones T, eds. *Quantification of brain function using PET*. San Diego: Academic Press, 1996:421-4.
- Woods RP, Mazziotta JC, Cherry SR. MRI-PET registration with automated algorithm. *J Comput Assist Tomogr* 1993;17:536-46.
- Woods RP, Cherry SR, Mazziotta JC. Rapid automated method for aligning and reslicing PET images. *J Comput Assist Tomogr* 1992;16:620-33.
- Talairach J, Tournoux P. *Co-planar stereotaxic atlas of the human brain*. New York: Thieme, 1988.
- Olivier A, Germano I, Cukiert A, Peters T. Frameless stereotaxy for surgery of the epilepsies: preliminary experience. *J Neurosurg* 1994;81:629-33.
- Harvey SA, Bowe JM, Hopkins IJ, Shield LK, Cook DJ, Berkovic SF. Ictal  $^{99\text{m}}\text{Tc}$ -HMPAO single positron emission computed tomography in children with temporal lobe epilepsy. *Epilepsia* 1993;34:869-77.
- Newton MR, Austin MC, Chan JG, McKay WJ, Rowe CC, Berkovic SF. Ictal SPECT using technetium-99m-HMPAO: methods for rapid preparation and optimal development of tracer during spontaneous seizures. *J Nucl Med* 1993;34:666-70.
- Markand ON, Salanova V, Worth R, Park H-M, Wellman HN. Comparative study of interictal PET and ictal SPECT in complex partial seizures. *Acta Neurol Scand* 1997;95:129-36.
- Theodore WH, Balish M, Leiderman D, Bromfield E, Sato S, Herscovitch P. Effect of seizures on cerebral blood flow measured with  $^{15}\text{O}$ - $\text{H}_2\text{O}$  and positron emission tomography. *Epilepsia* 1996;37:796-802.
- Collins RC, Kennedy C, Sokoloff L, Plum F. Metabolic anatomy of focal seizures. *Arch Neurol* 1976;33:536-42.
- Collins RC. Use of cortical circuits during focal penicillin seizures: an autoradiographic study with [ $^{14}\text{C}$ ]deoxyglucose. *Brain Res* 1978;150:487-501.
- Engel J Jr, Kuhl DE, Phelps ME, Rausch R, Nuwer M. Local cerebral metabolism during partial seizures. *Neurology* 1983;33:400-13.
- Prevett MC, Duncan JS, Jones T, Fish DR, Brooks DJ. Demonstration of thalamic activation during typical absence seizures using  $\text{H}_2$   $^{15}\text{O}$  and PET. *Neurology* 1995;45:1396-402.
- Nehlig A, Vergnes M, Waydelich R, et al. Absence seizures induce a decrease in cerebral blood flow: human and animal data. *J Cereb Blood Flow Metab* 1996;16:147-55.
- Matsumoto H, Ajmone Marsan C. Cortical cellular phenomena in experimental epilepsy: interictal manifestations. *Exp Neurol* 1964;9:286-304.
- Prince DA, Connors BW, Renardo LS. Mechanisms underlying

- interictal-ictal transitions. In: Delgado-Escueta AV, Wasterlain CG, Treiman DM, Porter RJ, eds. *Advances in neurology, vol 34: status epilepticus*. New York: Raven Press, 1983:177-87.
31. Matsumoto H, Ajmone Marsan C. Cortical cellular phenomena in experimental epilepsy: ictal manifestations. *Exp Neurol* 1964;9:305-26.
  32. Dichter MA, Ayala GF. Cellular mechanisms of epilepsy: a status report. *Science* 1987;237:157-64.
  33. Knowlton RC, Laxer KD, Ende G, et al. Presurgical multimodality neuroimaging in electroencephalographic lateralized temporal lobe epilepsy. *Ann Neurol* 1997;42:829-37.
  34. Henry TR, Engel J Jr, Mazziotta JC. Clinical evaluation of interictal fluorine-18-fluorodeoxyglucose PET in partial epilepsy. *J Nucl Med* 1993;34:1892-8.
  35. Theodore WH, Sato S, Kufta CV, Gaillard WD, Kelley K. FDG-positron emission tomography and invasive EEG: seizure focus detection and surgical outcome. *Epilepsia* 1997;38:81-6.
  36. Engel J, Brown WJ, Kuhl DE, Phelps ME, Mazziotta JC, Crandall PH. Pathological findings underlying focal temporal hypometabolism in partial epilepsy. *Ann Neurol* 1982;12:518-28.
  37. Bernadi S, Trimble MR, Frackowiak RSJ, Wise RJS, Jones T. An interictal study of partial epilepsy using positron emission tomography and the oxygen-15 inhalation technique. *J Neurol Neurosurg Psychiatry* 1983;46:473-7.
  38. Sloviter RS. The functional organization of the hippocampal dentate gyrus and its relevance to the pathogenesis of temporal lobe epilepsy. *Ann Neurol* 1994;35:640-54.
  39. Gaillard WD, Fazilat S, White S, et al. Interictal metabolism and blood flow are uncoupled in temporal lobe cortex of patients with complex partial epilepsy. *Neurology* 1995;45:1841-7.
  40. Fink GR, Pawlik G, Stefan H, Pietrzyk U, Wienhard K, Heiss WD. Temporal lobe epilepsy: evidence for interictal uncoupling of blood flow and glucose metabolism in temporomesial structures. *J Neurol Sci* 1996;137:28-34.
  41. Cowan JMA, Rothwell JC, Wise RJS, Marsden CD. Electrophysiological and positron emission studies in a patient with cortical myoclonus, epilepsy partialis continua and motor epilepsy. *J Neurol Neurosurg Psychiatry* 1986;49:796-807.
  42. Gloor P. Electroencephalography and the role of intracerebral depth electrode recordings in the selection of patients for surgical treatment of epilepsy. *Adv Epileptol* 1985;15:433-8.
  43. Fox PT, Raichle ME. Focal physiological uncoupling of cerebral blood flow and oxidative metabolism during somatosensory stimulation in human subjects. *Proc Natl Acad Sci USA* 1986;83:1140-4.
  44. DeYoe EA, Bandettini P, Neitz J, Miller D, Winans P. Functional magnetic resonance imaging (fMRI) of the human brain. *Neurosci Methods* 1994;54:171-87.
  45. Ramsey NF, Kirkby BS, Van Gelderen P, et al. Functional mapping of human sensorimotor cortex with 3D BOLD fMRI correlates highly with H<sub>2</sub>(15)O PET rCBF. *J Cereb Blood Flow Metab* 1996;16:755-64.
  46. Clark VP, Keil K, Maisog JM, Courtney S, Ungerleider LG, Haxby JV. Functional magnetic resonance imaging of human visual cortex during face matching: a comparison with positron emission tomography. *Neuroimage* 1996;4:1-15.